INTRANASAL FORMULATION CONTAINING SCOPOLAMINE AND METHOD OF TREATING MOTION SICKNESS

CROSS-REFERENCE TO RELATED APPLICATION

The present application claims priority to co-owned U.S. Provisional Application Serial No. 60/058,651 filed on 11 September 1997, the entire contents of which is hereby incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to pharmaceutical formulations containing scopolamine. More particularly, the present invention relates to nasal gel formulations for intranasal delivery of scopolamine, in particular, for preventing and/or treating motion sickness.

BACKGROUND OF THE INVENTION

Scopolamine, and more particularly, its salt Scopolamine Hydrobromide, have been investigated for a variety of clinical indications. Examples of potential uses for scopolamine include the treatment of general nausea and/or vomiting, motion sickness, peripheral vertigo, post operative conditions and the use as an anesthetic.

Several delivery routes have been utilized for administering scopolamine. These include oral, transdermal, buccal and intranasal administration. Oral and transdermal administration, however, do not provide a rapid onset of a therapeutically effective amount of scopolamine as determined by bioavailability studies. Oral administration of scopolamine is further complicated by first-pass metabolism in the liver which can significantly reduce

its bioavailability. Buccal administration of scopolamine has also been investigated. It has been reported, however, that the bioavailability from buccal administration does not significantly differ from oral administration.

Intranasal delivery of scopolamine has shown potential for the rapid onset of a therapeutically effective amount of the compound. For example, International Application No. PCT/US82/00941, published as WO 83/00286 on February 3, 1983 discloses treatment of sudden motion sickness with a nasal spray of scopolamine. While this reference discusses the rapid onset of scopolamine via the intranasal delivery route, there is no consideration of sustained delivery of scopolamine over a period of time or the storage stability of such a formulation.

While intranasal administration of various drugs such as scopolamine is known, the development of intranasal formulations to provide a therapeutically effective amount of a drug and the stability of the formulation over time is often unpredictable. While many drugs can be provided in intranasal formulations, the drug delivery offered by such formulations cannot be readily predicted and can dramatically differ between apparently similar formulations. Moreover, for an intranasal formulation of scopolamine to be effective in the prevention and treatment of acute conditions such as motion sickness, the ability to provide a therapeutically effective amount within 30 minutes, and desirably within 20 minutes, of administration is necessary. Likewise, considerations such as providing a therapeutically effective amount of the drug as soon as possible, maintaining a therapeutically effective level over a sustained amount of time and stability of the formulation over time must be balanced.

In considering the intranasal delivery of drugs, the pharmokinetics thereof are often considered. For example, ionization of a drug is believed to directly influence membrane penetration of the drug, and therefore, the absorption potential of the drug into the blood

stream. In particular, the ionization of a drug and therefore its absorption potential, is largely determined by the drug's dissociation constant, pK_a, as well as the pH of the solution in which the drug is dissolved. As reported by Mayersohn in Modern Pharmaceutics, Banker & Rhodes, 1979, Ch. 2, Pg. 40, basic compounds are best absorbed from alkaline solutions where $pH > pK_a$. Thus, it is generally believed that formulations for delivering basic drugs, in particular intranasal formulations, are best absorbed into the bloodstream when the basic drug is prepared in a formulation solution having a pH above the dissociation constant of the drug.

For example, scopolamine is known to be a basic drug. In order to provide effective membrane penetration and absorption through intranasal delivery, heretofor it has been understood that scopolamine hydrobromide should be formulated in a basic solution having a formulation pH greater than 7.6.

Intranasal formulations of scopolamine hydrobromide at pH levels below 7 have been investigated. For example, in "Absorption for Nasal Mucous Membrane: Systemic Effect of Hyoscine Following Intranasal Administration" by Tonndorf et al. in Ann. Oto. Rhino. Laryngol., vol. 62, 630, 1953, intranasal scopolamine spray formulations were prepared at a pH between 5.7-6.0. Moreover, U.S. Patent Application Serial No. 07/765,615 entitled "Intranasal Scopolamine Preparation and Method" discloses scopolamine formulations for intranasal spray delivery prepared at a pH of 4 ± 0.2. Both of these references disclose formulations which are inherently inefficient requiring 0.65 mg/ml and 0.4 mg/ml of scopolamine per dose, respectively. Such high dosages are wasteful of drug, add unnecessary cost to consumer and may cause undesirable side effects.

Accordingly, there is a need in the art for intranasal formulations that provide a therapeutically effective amount of scopolamine into the bloodstream within a relatively

short time period (e.g., 30 minutes or less), that provide therapeutically effective levels of scopolamine for a sustained amount of time, that do not degrade over time and are not irritating to the nasal cavity.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide an intranasal formulation for preventing and/or treating nausea and/or vomiting and other symptoms associated with motion sickness.

It is a further object of the invention to provide a scopolamine nasal formulation capable of prolonged shelf storage.

It is a further object of the invention to provide an intranasal formulation capable of achieving rapid plasma concentrations without achieving dangerous peak plasma concentrations.

In the efficient attainment of these and other objects, the present invention provides an intranasal formulation including scopolamine in a pharmaceutically acceptable carrier. The formulation has a pH below about 4.0, desirably at or below about 3.5, and a salt concentration below about 200 mM, desirably at or below 100 mM, such as for example at or below 50 mM. Desirably, the formulation incorporates polyvinyl alcohol therein. Preferably the carrier is provided as an intranasal gel, with the polyvinyl alcohol acting as a gelling agent for the composition. The scopolamine is preferably provided as a pharmaceutically acceptable salt, such as for example, scopolamine hydrobromide.

The present invention also relates to a method of preventing and/or treating nausea including administering intranasally to a mammal an effective amount of scopolamine, chemically modified equivalents and pharmaceutical salts thereof in a pharmaceutically acceptable carrier at a pH below about 4.0 and a salt concentration below about 200 mM, with the carrier incorporating polyvinyl alcohol.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph representing average plasma concentration over time of intranasal gel formulations incorporating different gelling agents.

Figure 2 is a graph representing product degradation as a function of the percentage formulation molarity over time for intranasal gel formulations.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is an intranasal formulation for delivery of scopolamine. As used herein, "intranasal formulation" is intended to include a pharmaceutically acceptable carrier which incorporates the active agent, i.e., scopolamine. For purposes of the present invention, "pharmaceutical carrier" includes nasal sprays, nasal drops, gels, ointments, creams and the like. The present formulations may be administered using, for example, a nasal tampon or a nasal sponge containing the present formulation. Desirably, however, scopolamine is delivered in a gel formulation as set forth in more detail below.

Polyvinyl alcohol (PVA) is known to enhance viscosity. It is well known that PVA should be used in a pH range of about 5 - 8. Thus, one skilled in the art would not be motivated to formulate PVA-containing pharmaceutical compositions at a pH lower than 5

and would reject such a composition as a pharmaceutical carrier for, e.g., scopolamine. Surprisingly, it has been demonstrated in the present invention that gel formulations of scopolamine having PVA as the main gelling agent provide products with excellent stability which are superior to prior art spray formulations, as well as gel formulations using methyl cellulose. Thus, nasal gel preparations of scopolamine according to the present invention are prepared using PVA. The amount of PVA that can be used in the present invention can vary depending upon the specific formulation. In particular, the amount of PVA contained in the present invention is that amount which is sufficient to form a pharmaceutically acceptable gel. Desirably, PVA is present in the present formulations up to about 30%, more desirably, up to about 20%, such as for example up to about 10%.

Gel systems having as a main component a composition having similar properties to PVA and which provide results substantially as set forth in the Examples below are also contemplated by the present invention. For example, gelling agents including the following can be used as a substitute for or in addition to PVA: alginates, gums, starches, polyacrylates, dextrans, chitosans and mixtures thereof.

In the present invention, scopolamine is combined with the pharmaceutical carrier at a pH of about 4. Desirably, scopolamine is combined with the pharmaceutical carrier at or below about pH 3.5.

In addition to maintaining the pH of the present formulation at or below 4, the salt concentration thereof must be maintained at or below about 200 mM. Desirably, the salt concentration is maintained at or below about 100 mM, such as for example at or below about 50 mM.

For purposes of the present invention, the term "scopolamine" as used herein is intended to include those pharmaceutically active scopolamine compositions set forth in The

Merck Index (11th Edition on page 8363) including [7(S)-(1α,2β,4β,5α,7β)]-α-(Hydroxymethyl)benzeneacetic acid 9-methyl-3-oxa-9-azatricyclo-[3.3.$0^{2,4}$]non-7-yl ester and 6β,7β-epoxy-1αH,5αH-tropan-3α-ol (-)-tropate. Moreover, as used herein, "scopolamine" also includes pharmaceutical salts and hydrated forms, as well as all chemically modified equivalents thereof. Scopolamine hydrobromide or scopolammonium bromide ($C_{17}H_{22}BrNO_4 \cdot 3H_2O$), scopolamine hydrochloride ($C_{17}H_{22}ClNO_4$), methscopolamine bromide and methscopolamine nitrate ($C_{18}H_{24}N_2O_7$) are examples of pharmaceutical salts which can be used in accordance with the present invention. As used herein, "chemically modified equivalents" is intended to include compositions which may have a chemical structure that differs from scopolamine but which functions in a similar manner in the body, such as for example prodrugs, analogs, biologically active fragments and the like.

Such compositions have clinical utility to prevent and treat nausea and/or vomiting associated with, for example motion sickness. In addition, such compositions can be used as a sedative and as a pre-anesthetic. The present formulations, thus can be used to treat and/or prevent a variety of symptoms.

As set forth above, the present formulations can be used to both prevent and treat nausea and/or vomiting induced by motion sickness. Thus, the present formulations can be administered to a mammal prior to any symptoms associated with motion sickness and can prevent nausea and/or vomiting which are often symptoms thereof. Moreover, once onset of motion sickness symptoms has occurred in a patient, the present formulations can be administered to the patient and will provide alleviation or substantial decrease of the nausea and/or vomiting associated with motion sickness.

In the present invention, many other excipients, known from the pharmaceutical literature, may be added to the formulations, such as preservatives, surfactants, co-solvents,

adhesives, antioxidants, buffers, viscosity enhancing agents and agents to adjust the pH or the osmolarity.

The various forms of the intranasal formulations set forth above can optionally include a buffer to maintain the pH of the scopolamine formulation, a pharmaceutically acceptable thickening agent, humectant and surfactant. Desirably, the pH of the buffer is selected to maintain the stability of scopolamine. In particular, the pH of the buffer is selected to optimize the stability of the scopolamine in the present inventive formulations. As set forth previously, the pH of the buffer is desirably below about 4, more desirably at or below about 3.5. Buffers that are suitable for use in the present invention include, for example, hydrochloride, acetate, citrate, carbonate and phosphate buffers.

The viscosity of the compositions of the present invention can be maintained at a desired level using a pharmaceutically acceptable thickening agent. Thickening agents that can be used in accordance with the present invention include for example, xanthan gum, carbomer, polyvinyl alcohol, alginates, acacia, chitosans and mixtures thereof. The concentration of the thickening agent will depend upon the agent selected and the viscosity desired.

The compositions of the present invention also include a tolerance enhancer to reduce or prevent drying of the mucus membrane and to prevent irritation thereof. Suitable tolerance enhancers that can be used in the present invention include, for example, humectants, sorbitol, propylene glycol, mineral oil, vegetable oil and glycerol; soothing agents, membrane conditioners, sweeteners and mixtures thereof. The concentration of the tolerance enhancer(s) in the present compositions will also vary with the agent selected.

In order to enhance absorption of the scopolamine through the nasal mucosa, a

therapeutically acceptable surfactant may be added to the intranasal formulation. Suitable surfactants that can be used in accordance with the present invention include, for example, polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides, such as for example, Tween 80, Polyoxyl 40 Stearate, Polyoxy ethylene 50 Stearate, fusidates, bile salts and Octoxynol. Suitable surfactants include non-ionic, anionic and cationic surfactants. These surfactants can be present in the intranasal formulation in a concentration ranging from about 0.001% to about 20% by weight.

In the present invention other optional ingredients may also be incorporated into the nasal delivery system provided they do not interfere with the action of the scopolamine or significantly decrease the absorption of scopolamine across the nasal mucosa. Such ingredients can include, for example, pharmaceutically acceptable excipients and preservatives. The excipients that can be used in accordance with the present invention include, for example, bio-adhesives and/or swelling/thickening agents.

In the present invention, any other suitable absorption enhancers as known in the art may also be used.

Preservatives can also be added to the present compositions. Suitable preservatives that can be used with the present compositions include, for example, benzyl alcohol, parabens, thimerosal, chlorobutanol and benzalkonium, with benzalkonium chloride being preferred. Typically, the preservative will be present in the present compositions in a concentration of up to about 2% by weight. The exact concentration of the preservative, however, will vary depending upon the intended use and can be easily ascertained by one skilled in the art.

Another embodiment of the present invention is an intranasal formulation for

preventing or treating motion sickness. This formulation includes scopolamine hydrobromide in a PVA gel solution at a pH at or below about 3.5 and a salt concentration below about 100 mM. In this embodiment, the PVA gel solution can include mixtures of other gelling agents or bio-adhesives, such as for example, alginates, gums, starches, polyacrylates, dextrans, chitosans and mixtures thereof. Moreover, the PVA gelling agent can be replaced with other similar gelling/bio-adhesives provided that such agents produce the surprising results as set forth in the examples of the present invention.

Another embodiment of the present invention is a method of preventing and/or treating nausea and/or vomiting. This method includes administering intranasally to a mammal an effective amount of scopolamine, chemically modified equivalents and pharmaceutical salts thereof in a pharmaceutically acceptable carrier at a pH at or below about 4.0 with a salt concentration at or below about 200 mM. The pharmaceutically acceptable carrier is desirably PVA, however, other gelling/bio-adhesives which provide results similar to those set forth in the present experimental examples are also contemplated. Examples of such gelling/bio-adhesives include, alginates, gums, starches, polyacrylates, dextrans, chitosans and mixtures thereof. Moreover, the pharmaceutically acceptable carrier can include PVA and mixtures of other appropriate gelling/bio-adhesives provided the formulation produces superior pharmacokinetic profiles along the lines set forth in the Examples.

The pharmaceutically acceptable carrier of the present invention is specifically designed for intranasal administration. Such formulations are safe and effective for intranasal delivery to mammals, including humans. Formulations of such carriers are well known in the art and specific examples thereof are provided below.

In the present embodiment of the invention, the salt concentration is desirably at or

below 100 mM, such as for example, 50 mM. As set forth above, the pH of the present formulation is desirably at or below about 3.5.

The following examples are set forth to illustrate the formulations of the present invention, as well as the surprising results achieved therewith. These examples are provided for purposes of illustration only and are not intended to be limiting in any sense.

EXAMPLE 1

Inventive and Comparative Formulations

Example 1 sets forth a comparative intranasal scopolamine hydrobromide nasal gel formulation containing methyl cellulose with a buffer concentration of 25 mM (Formulation 1) and three inventive intranasal scopolamine hydrobromide nasal gel formulations according to the present invention containing PVA at 20, 50 and 100 mM buffer concentrations (Formulations 2, 3 and 4, respectively).

Nasal gel Formulation 1 containing a methyl cellulose gelling agent at a pH of about 3.5 and having a scopolamine concentration of about 0.2 mg/0.1gm at a buffer concentration of 0.025M (25 mM) was prepared as follows:

Formulation 1 - Methyl Cellulose (25 mM)

Composition	Quantity - 100mL(Gm)
Scopolamine Hydrobromide, USP	0.20
Citric Acid Anhydrous, USP	0.37
Sodium Citrate Dihydrate, USP	0.17
Sodium Metabisulfite, NF	0.1
Glycerine (96%), USP	5.0
Methyl cellulose (4000 cps), USP	2.0
Benzalkonium Chloride (50%), NF	0.04
Purified Water, USP	100 Q.S.

Nasal gel Formulation 2 containing a PVA gelling agent at a pH of about 3.5 and having a scopolamine concentration of about 0.2 mg/0.1gm at a buffer concentration of 0.02M (20 mM) was prepared as follows:

Formulation 2 - PVA (20 mM)

Composition	Quantity - 100mL(Gm)
Scopolamine Hydrobromide, USP	0.20
Citric Acid Anhydrous, USP	0.32
Sodium Citrate Dihydrate, USP	0.098
Sodium Metabisulfite, NF	0.1
Glycerine (96%), USP	5.0
Polyvinyl Alcohol, USP	10.0
Benzalkonium Chloride (50%), NF	0.04
Purified Water, USP	100 Q.S.

Formulation 3 - PVA (50 mM)

Composition	Quantity - 100mL(Gm)
Scopolamine Hydrobromide, USP	0.20
Citric Acid Anhydrous, USP	0.73
Sodium Citrate Dihydrate, USP	0.34
Sodium Metabisulfite, NF	0.1
Glycerine (96%), USP	5.0
Polyvinyl Alcohol, USP	10.0
Benzalkonium Chloride (50%), NF	0.20
Purified Water, USP	100 Q.S.

Formulation 4 - PVA (100 mM)

Composition	Quantity - 100mL(Gm)
Scopolamine Hydrobromide, USP	0.20
Citric Acid Anhydrous, USP	1.42
Sodium Citrate Dihydrate, USP	0.76
Sodium Metabisulfite, NF	0.1
Glycerine (96%), USP	5.0
Polyvinyl Alcohol, USP	10.0
Benzalkonium Chloride (50%), NF	0.04
Purified Water, USP	100 Q.S.

EXAMPLE 2

Comparison of Methyl Cellulose vs. PVA Formulations: Scopolamine Absorption

Example 2 is a comparison of scopolamine absorption into the blood stream from Formulation 1 (methyl cellulose at 25 mM buffer concentration) vs. Formulation 2 (PVA at 20 mM buffer concentration). Nasal gel formulations were prepared based on Formulations 1-2 set forth above. These Formulations were adjusted to a pH value of about 3.5 with citric acid solution or sodium citrate solution as needed.

The nasal gel Formulations 1 and 2 were administered intranasally to 10 healthy humans. The plasma concentration of scopolamine free base was measured in these individuals over time for a period of 240 minutes by LC/MS/MS. The average results of these measurements are shown in Table 1, and depicted in Figure 1.

Table 1

Comparison of Methyl Cellulose vs. PVA Formulations: Scopolamine Absorption

Time (minutes)	Formulation 1[#]	Formulation 2[#]
0	0 ± 0	0 ± 0
5	28.4 ± 45.1	80.7 ± 58.3
10	106 ± 157	138.6 ± 86.7
20	136 ± 144	203 ± 124
30	144 ± 100	219 ± 112
45	152 ± 119	220 ± 111
60	137 ± 106	188 ± 127
120	119 ± 99.0	123 ± 81.8
240	44.1 ± 37.5	58.3 ± 39.7
C_{max}* (pg/ml)	204 ± 161	248 ± 123
T_{max}* (minutes)	45.5 ± 31.2	35.5 ± 12.8

[#]Average Plasma Concentration of Scopolamine Free Base (pg/ml).

* C_{max} and T_{max} values represent an average of the respective C_{max} and T_{max} values obtained for each patient.

As can be seen from these results, absorption of scopolamine into the blood was within acceptable limits as recognized by those skilled in the art for both Formulations 1 and 2.

A comparison of the plasma concentrations of scopolamine free base for Formulation 1 (methyl cellulose) with Formulation 2 (PVA) demonstrates the unexpected and surprising results achieved through the present invention. As is clearly evident from Figure 1 which is a graphic representation of the data set forth in Table 1, the average plasma concentration over time of Formulation 1 (methyl cellulose) was considerably below that of Formulation 2 (PVA). Thus, the intranasal formulation according to the

present invention (Formulation 2) achieves significantly higher scopolamine absorption into the blood compared to intranasal Formulation 1 (methyl cellulose). Additionally, rapid onset of the drug is achieved with the present inventive formulation (Formulation 2), as is evidenced by the graph which shows scopolamine free base concentrations of Formulation 2 which according to the present invention more than doubled that of the Formulation 1 in 5 minutes.

EXAMPLE 3

Comparison of Stability of PVA and Methyl Cellulose Intranasal Formulations

This Example provides stability data comparing Formulation 1 (methyl cellulose) with Formulation 2 (PVA) at various temperatures and relative humidities.

For purposes of the present examples, formulations having unacceptable stability exhibited more than 1% degradation of product resulting in the formation of tropic acid over 6 months of storage at 40°C and 75% humidity in accordance with generally accepted FDA guidelines for minimum stability.

Nasal gel Formulations 1 and 2 having a scopolamine concentration of 0.2 mg/0.1gm at a buffer concentration of 0.025M (25mM) and 0.02 (20 mM), respectively were prepared in accordance with the formulations of Example 1.

A. Stability at 40°C/75% RH

Formulations 1 and 2 were adjusted to a pH value of about 3.5 with citric acid solution or sodium citrate solution as needed. The respective formulations were stored in a standard drug container in both upright and inverted positions at a temperature of 40° C and 75 % relative humidity, over time for a period of 6 months. Various measurements were taken to represent stability of each formulation, including Scopolamine HBr content

as a percentage, degradation of the product represented by the percentage of tropic acid appearing in the formulation and viscosity. The results are set forth in Table 2 (Formulation 1 - methyl cellulose) and Table 3 (Formulation 2 - PVA) below.

Table 2

Methyl Cellulose (25 mM)

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.48	102.6	not detectable	4393
1	Upright	3.30	101.0	not quantifiable	1452
1	Inverted	3.31	101.7	not quantifiable	1341
2	Upright	3.13	102.3	not quantifiable	--
2	Inverted	3.13	104.1	not quantifiable	--
3	Upright	3.11	106.6	0.23	--
3	Inverted	3.09	104.2	0.23	--
6	Upright	3.03	101.4	0.45	206
6	Inverted	3.08	102.3	0.45	259

Table 3

PVA (20 mM)

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.64	104.0	not detectable	1711
1	Upright	3.52	100.9	not quantifiable	1714
1	Inverted	3.50	100.8	not quantifiable	1761
2	Upright	3.49	100.8	not quantifiable	--
2	Inverted	3.46	101.0	not quantifiable	--
3	Upright	3.31	102.8	0.21	--
3	Inverted	3.29	103.5	0.22	--
4	Upright	3.09	102.0	0.27	--
4	Inverted	3.11	103.0	0.27	--
5	Upright	3.08	102.[illegible]	0.33	--
5	Inverted	3.06	102.9	0.34	--
6	Upright	3.03	105.4	0.50	1564
6	Inverted	3.03	102.6	0.40	1618

As is evident from the data depicted in Table 2, Formulation 1 (methyl cellulose) provides stability with respect to scopolamine HBr content, maintaining 101.4% and 102.3 % for upright and inverted containers, respectively, over 6 months storage. Moreover, the degradation of this gel formulation over time is within acceptable limits, demonstrated by 0.45 percent of tropic acid in the formulation after 6 months. The viscosity of Formulation 1 (methyl cellulose), however, rapidly decreased from an initial level of 4393 cts to 1452 cts and 1341 cts for upright and inverted containers, respectively, after only 1 month of storage, and further decreasing to 206 cts and 209 cts for upright and inverted containers, respectively, after 6 months storage, demonstrating an unacceptable change in viscosity for stability.

As is evident from the data depicted in Table 3, Formulation 2 (PVA) remains both chemically and physically stable over the entire 6 month period, as evidenced by the Scopolamine HBr content, degradation product and viscosity of the formulation remaining within acceptable ranges, even after 6 months of storage time.

B. Stability at 30°C/60% RH

The stability of Formulations 1 and 2 was investigated at a temperature of 30°C at 60% relative humidity over the course of 6 months substantially as set forth above. The data from this investigation is set forth below in Table 4 (Formulation 1 - methyl cellulose) and Table 5 (Formulation 2 -PVA):

Table 4

Methyl Cellulose (25 mM)

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.48	102.6	not detectable	4393
1	Upright	3.40	102.3	not detectable	-
1	Inverted	3.42	102.7	not detectable	-
2	Upright	3.28	104.6	not detectable	-
2	Inverted	3.26	104.0	not detectable	-
3	Upright	3.26	106.9	not quantifiable	2082
3	Inverted	3.24	107.5	not quantifiable	2233
6	Upright	3.15	103.4	not quantifiable	1083
6	Inverted	3.16	103.2	not quantifiable	1305

Table 5

PVA (20 mM)

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.64	104.0	not detectable	1711
1	Upright	3.60	101.5	not detectable	--
1	Inverted	3.59	100.5	not detectable	--
2	Upright	3.63	100.7	not detectable	--
2	Inverted	3.66	101.7	not detectable	--
3	Upright	3.51	104.7	not quantifiable	1665
3	Inverted	3.52	104.3	not quantifiable	1637
6	Upright	3.34	105.4	not quantifiable	1633
6	Inverted	3.40	104.2	not quantifiable	1595

As is evident from the data depicted in Table 4, Formulation 1 (methyl cellulose) stored at 30° C and 60% relative humidity provides stability with respect to scopolamine HBr content, maintaining 103.4% and 103.2 % for upright and inverted containers, respectively, over 6 months storage. Moreover, the degradation of this gel formulation over time is within acceptable limits, demonstrated by no quantifiable percent of tropic acid in the formulation after 6 months. The viscosity of Formulation 1, however, again rapidly decreased from an initial level of 4393 cts to 2082 cts and 2233 cts for upright and inverted containers, respectively, after 3 months of storage, and further decreased to 1083 cts and 1305 cts for upright and inverted containers, respectively, after 6 months storage, demonstrating an unacceptable change in viscosity for stability.

As is evident from the data depicted in Table 5, Formulation 2 (PVA) remains both chemically and physically stable over the entire 6 month period, as evidenced by the Scopolamine HBr content, degradation product and viscosity of the formulation remaining within acceptable ranges, even after 6 months of storage time.

C. **Stability at 25°C/60% RH**

The stability of Formulations 1 and 2 was investigated at a temperature of 25°C at 60% relative humidity over the course of 6 months substantially as set forth above. The data from this investigation is set forth below in Table 6 (Formulation 1 - methyl cellulose) and Table 7 (Formulation 2 -PVA):

Table 6

Methyl Cellulose (25 mM)

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.48	102.6	not detectable	4393
3	Upright	3.26	107.0	not detectable	--
3	Inverted	3.32	102.4	not detectable	--
6	Upright	3.19	103.2	not quantifiable	1755
6	Inverted	3.19	103.2	not quantifiable	2129

Table 7

PVA (20 mM)

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.64	104.0	not detectable	1711
3	Upright	3.55	104.4	not detectable	--
3	Inverted	3.56	103.8	not detectable	--
6	Upright	3.46	104.0	not quantifiable	1640
6	Inverted	3.47	104.6	not quantifiable	1640

As is evident from the data depicted in Table 6, Formulation 1 (methyl cellulose)

provides stability with respect to scopolamine HBr content, maintaining 103.2 % for both the upright and inverted containers over 6 months storage. Moreover, the degradation of this gel formulation over time is within acceptable limits, demonstrated by no quantifiable percent of tropic acid in the formulation after 6 months. The viscosity of Formulation 1 (methyl cellulose), however, again decreased from an initial level of 4393 cts to 1755 cts and 2129 cts for upright and inverted containers, respectively, after 6 months storage, demonstrating an unacceptable change in viscosity for stability.

As is evident from the data depicted in Table 7, Formulation 2 (PVA) remains both chemically and physically stable over the entire 6 month period, as evidenced by the Scopolamine HBr content, degradation product and viscosity of the formulation remaining within acceptable ranges, even after 6 months of storage time.

D. Stability at 15°C/40% RH

The stability of Formulations 1 and 2 was investigated at a temperature of 15°C at 40% relative humidity over the course of 6 months substantially as set forth above. The data from this investigation is set forth below in Table 8 (Formulation 1 - methyl cellulose) and Table 9 (Formulation 2 -PVA):

Table 8

Methyl Cellulose (25 mM)

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.48	102.6	not detectable	4393
3	Upright	3.35	106.5	not detectable	--
3	Inverted	3.33	105.9	not detectable	--
6	Upright	3.30	105.6	not detectable	3418
6	Inverted	3.33	103.7	not detectable	3220

Table 9

PVA (20 mM)

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.64	104.0	not detectable	1711
3	Upright	3.62	103.2	not detectable	--
3	Inverted	3.62	103.4	not detectable	--
6	Upright	3.56	104.2	not detectable	1709
6	Inverted	3.55	104.1	not detectable	1839

As is evident from the data depicted in Table 8, even with Formulation 1 (methyl cellulose) stored at 15° C and 40% relative humidity, stability with respect the viscosity of the formulation decreased from an initial level of 4393 cts to 3418 cts and 3220 cts for upright and inverted containers, respectively, after 6 months storage. Thus, even under cold storage conditions, the stability of Formulation 1 (methyl cellulose) was inadequate, as demonstrated by an unacceptable change in viscosity.

As is evident from the data depicted in Table 9, Formulation 2 (PVA) remains both chemically and physically stable over the entire 6 month period, as evidenced by the Scopolamine HBr content, degradation product and viscosity of the formulation remaining within acceptable ranges, even after 6 months of storage time.

Thus, these data support the surprising conclusion that Formulation 2 containing PVA as a gelling agent is consistently more stable compared to Formulation 1 containing methyl cellulose as a gelling agent over the entire 6 month investigational period at a variety of temperatures and relative humidities.

EXAMPLE 4

Effect of Molarity on Stability of PVA Formulations (20 mM, 50 mM and 100 mM)

Example 4 is a study of the effect of different molarities on PVA stability over time. In particular, Formulations 2, 3 and 4 were prepared substantially as set forth in Example 1 with molarities of 20 mM, 50 mM and 100 mM, respectively.

Formulations 2, 3 and 4 were adjusted to a pH value of about 3.5 with citric acid solution or sodium citrate solution as needed. The respective formulations were stored in a standard drug container in both upright and inverted positions at various temperatures and relative humidity, over time for a period of 6 months. Various measurements were taken to represent stability of each formulation, including Scopolamine HBr content as a percentage, degradation of the product represented by the percentage of tropic acid appearing in the formulation and viscosity. The results are set forth in Tables 10 - 21 below.

Table 10

Formulation 2 at 40°C/75% Relative Humidity (%RH)

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.64	104.0	not detectable	1711
1	Upright	3.52	100.9	not quantifiable	1714
1	Inverted	3.50	100.8	not quantifiable	1761
2	Upright	3.49	100.8	not quantifiable	--
2	Inverted	3.46	101.0	not quantifiable	--
3	Upright	3.31	102.8	0.21	--
3	Inverted	3.29	103.5	0.22	--
4	Upright	3.09	102.0	0.27	--
4	Inverted	3.11	103.0	0.27	--
5	Upright	3.08	102.7	0.33	--
5	Inverted	3.06	102.9	0.34	--
6	Upright	3.03	105.4	0.50	1564
6	Inverted	3.03	102.6	0.40	1618

Table 11

Formulation 3 at 40°C/75% RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.50	103.1	not detectable	1705
1	Upright	3.50	104.5	not quantifiable	1659
1	Inverted	3.40	102.2	not quantifiable	1696
2	Upright	3.40	102.5	0.22	--
2	Inverted	3.40	103.0	0.21	--
3	Upright	3.40	104.2	0.32	--
3	Inverted	3.40	104.5	0.31	--
4	Upright	3.34	103.0	0.43	--
4	Inverted	3.32	103.0	0.41	--
5	Upright	3.33	103.6	0.56	--
5	Inverted	3.32	103.4	0.60	--
6	Upright	3.32	104.5	0.68	1579
6	Inverted	3.30	103.0	0.66	1709

Table 12

Formulation 4 at 40°C/75% RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.52	106.5	not detectable	1924
1	Upright	3.58	102.9	not quantifiable	1751
1	Inverted	3.57	103.6	not quantifiable	1755
2	Upright	3.49	102.5	0.35	--
2	Inverted	3.48	102.7	0.33	--
3	Upright	3.44	103.5	0.50	--
3	Inverted	3.44	103.5	0.48	--
6	Upright	3.39	101.5	1.00	1747
6	Inverted	3.39	101.4	0.99	1701

Table 13

Formulation 2 at 30°C/60% RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.64	104.0	not detectable	1711
1	Upright	3.60	101.5	not detectable	--
1	Inverted	3.59	101.5	not detectable	--
2	Upright	3.63	100.7	not detectable	--
2	Inverted	3.66	101.7	not detectable	--
3	Upright	3.51	104.7	not quantifiable	1665
3	Inverted	3.52	104.3	not quantifiable	1637
6	Upright	3.34	105.4	not quantifiable	1633
6	Inverted	3.40	104.2	not quantifiable	1595

Table 14

Formulation 3 at 30°C/60% RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.50	103.1	not detectable	1705
1	Upright	3.60	104.4	not detectable	1693
1	Inverted	3.60	104.4	not detectable	1884
2	Upright	3.50	104.0	not quantifiable	--
2	Inverted	3.50	103.1	not quantifiable	--
3	Upright	3.50	105.3	not quantifiable	--
3	Inverted	3.50	104.5	not quantifiable	--
6	Upright	3.46	104.7	0.68	1610
6	Inverted	3.45	104.3	0.66	1618

Table 15

Formulation 4 at 30°C/60% RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.52	106.5	not detectable	1924
1	Upright	3.57	104.6	not quantifiable	--
1	Inverted	3.59	103.8	not quantifiable	--
2	Upright	3.52	103.0	not quantifiable	--
2	Inverted	3.51	103.7	not quantifiable	--
3	Upright	3.48	104.5	not quantifiable	1810
3	Inverted	3.50	104.8	not quantifiable	1776
6	Upright	3.46	103.3	0.35	1770
6	Inverted	3.46	103.7	0.35	1709

Table 16

Formulation 2 at 25°C/60%RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.64	104.0	not detectable	1711
3	Upright	3.55	104.4	not detectable	--
3	Inverted	3.56	103.8	not detectable	--
6	Upright	3.46	104.0	not quantifiable	1640
6	Inverted	3.47	104.6	not quantifiable	1640

Table 17

Formulation 3 at 25°C/60%RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.50	103.1	not detectable	1705
3	Upright	3.50	104.8	not quantifiable	--
3	Inverted	3.50	104.3	not quantifiable	--
6	Upright	3.50	104.8	not quantifiable	1633
6	Inverted	3.42	104.4	not quantifiable	1938

Table 18

Formulation 4 at 25°C/60%RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.52	106.5	not detectable	1924
3	Upright	3.51	104.3	not quantifiable	--
3	Inverted	3.50	105.0	not quantifiable	--
6	Upright	3.47	103.7	0.24	1770
6	Inverted	3.48	103.7	0.24	1701

Table 19

Formulation 2 at 15°C/40%RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.64	104.0	not detectable	1711
3	Upright	3.62	103.2	not detectable	--
3	Inverted	3.62	103.4	not detectable	--
6	Upright	3.56	104.2	not detectable	1709
6	Inverted	3.55	104.1	not detectable	1839

Table 20

Formulation 3 at 15°C/40%RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.50	103.1	not detectable	1705
3	Upright	3.50	103.4	not detectable	--
3	Inverted	3.50	104.7	not detectable	--
6	Upright	3.51	104.1	not quantifiable	1701
6	Inverted	3.49	104.8	not quantifiable	1686

Table 21

Formulation 4 at 15°C/40%RH

TIME (Months)	Container Position	pH	Scopolamine HBr (% LC)	Degradation Product (Tropic Acid, %LC)	Viscosity (cts)
initial	--	3.52	106.5	not detectable	1924
3	Upright	3.51	105.5	not detectable	--
3	Inverted	3.52	105.6	not detectable	--
6	Upright	3.49	104.5	not quantifiable	1846
6	Inverted	3.49	104.0	not quantifiable	1801

Tables 10-21 above demonstrate that Formulations 2 - 4 according to the present invention remain both chemically and physically stable when stored at varying conditions of temperature and humidity as measured by scopolamine HBr content, degradation product and viscosity. Each of these parameters remained within acceptable limits as recognized by one skilled in the art even after 6 months of storage. The data indicate, however, that at PVA concentrations at about 100 mM (Formulation 4) the degradation product as represented by the % tropic acid is at 1.00% and 0.99% after 6 months of storage (Table 12). Thus, the 100 mM formulation (Formulation 4) approached

unacceptable levels representing chemical instability thereof at elevated temperatures for prolonged storage periods. Thus, the data suggest that nasal formulations at PVA concentrations above 100 mM are not likely to be useful due to chemical instability.

EXAMPLE 4

Stability of PVA Formulations at Different Buffer Concentrations

Example 4 is a direct comparison of the effect of the buffer concentration on the PVA Formulations (Formulations 2, 3 and 4) at 40°C/75%RH. This data is set forth in Table 22 and graphed in Figure 2, which demonstrates product degradation as a function of the percentage of tropic acid in the formulation over time.

Table 22

Effect of Buffer Concentration on Stability of PVA Formulations

Formulation #	Buffer Molarity (mM)	Tropic Acid (% LC) (ND=not detectable; NQ=not quantifiable)						
		Initial	1 month	2 month	3 month	4 month	5 month	6 month
2	20	ND	NQ	NQ	0.21	0.27	0.33	0.50
3	50	ND	NQ	0.22	0.32	0.43	0.56	0.68
4	100	ND	0.20	0.35	0.50	--	--	1.00

As is evident from Table 22 and Figure 2, Formulations 2, 3 and 4 prepared according to the present invention with PVA remain physically and chemically stable for up to 6 months. In fact, the formulations at 20 mM and 50 mM, as represented in Tables 10 and 11, respectively, provide excellent stability results even at the 6 month storage time, while Formulation 4 (100 mM) as represented by Table 12, approaches unstable limits of 1.00 % tropic acid, representing chemical degradation at the 6 month storage date. Moreover, it can be recognized from these data that formulations incorporating PVA prepared at a pH of about 3.5 and at concentrations above 100 mM lose chemical stability during storage.

Example 5

Comparison of Stability of Methyl Cellulose vs. PVA Formulations as a Function of Viscosity

Example 5 is a direct comparison of Formulation 1 (methyl cellulose) and Formulation 2 (PVA) at 40°C/75%RH highlighting the viscosity data as set forth in Table 23 below.

Table 23

Methyl Cellulose vs. PVA Formulations as a Function of Viscosity

Formulation #	Viscosity (cts)		
	Initial	1 month	6 month
1	4393	1452	206
2	1711	1714	1564

As is evident from a review of the results of Table 23, the nasal gel formulation prepared according to the present invention with polyvinyl alcohol as a gelling agent in a formulation at about pH 3.5 and concentration of 20 mM (Formulation 2) maintains a substantially constant viscosity over time, thus evidencing that such formulations remain chemically and physically stable for periods of 6 months. The nasal gel formulation prepared with methyl cellulose as a gelling agent in a formulation at about pH 3.5 and concentration of 25 mM (Formulation 1) demonstrates a significant decrease in viscosity after only one month of storage, with a remarkable decrease after 6 months of storage, thus evidencing that such a formulation is chemically and physically unstable.

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention and all such modifications are intended to be included within the scope of the following claims.